The impact of MenAfriVac in nine countries of the African meningitis belt, 2010-2015: an analysis of surveillance data

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Abstract

Background In preparation for the introduction of MenAfriVac®, a meningococcal group A conjugate vaccine developed for the African meningitis belt, an enhanced meningitis surveillance network was established. We analysed surveillance data on suspected and confirmed cases of meningitis to quantify vaccine impact.

Methods Surveillance data from - (Benin, Burkina Faso, Chad, Côte d'Ivoire, Ghana, Mali, Niger, Nigeria, Togo)collected and curated by the World Health Organisation Inter-country Support Team between 2005-2015 were included. The incidence rate ratios of suspected and confirmed cases in vaccinated and unvaccinated populations were estimated using -negative binomial regression models. The relative risk of districts reaching the epidemic threshold of 10 per 100,000 per week was estimated according to district vaccination status.

Findings The incidence of suspected meningitis cases declined by 57% (95%CI 55-59%) in vaccinated compared to unvaccinated populations, with some heterogeneity observed by country. We observed a similar 59% decline in the risk of a district reaching the epidemic threshold. In fully vaccinated populations the incidence of confirmed group A disease was reduced by >99%. The incidence rate ratio for non-A serogroups was higher after completion of MenAfriVac® campaigns (IRR 2.76, 95% CI 1.21, 6.30).

Interpretation MenAfriVac® introduction has led to considerable reductions in the incidence of suspected meningitis and epidemic risk and a dramatic impact on confirmed group A meningococcal meningitis. It is important to continue strengthening surveillance to monitor vaccine performance and remain vigilant against threats from other meningococcal serogroups and other pathogens.

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Introduction

Countries in the "African meningitis belt", an area in sub-Saharan Africa that stretches from Senegal in the west to Ethiopia in the east, are susceptible to devastating outbreaks of meningococcal meningitis, with population attack rates as high as 1% during major epidemics[1]. Most epidemics in the past have been due to group A *Neisseria meningitidis* (NmA), but epidemics due to other serogroups (NmC, NmW, NmX) have been recorded[2-4]. An enhanced meningitis surveillance network was established across the meningitis belt in 2003[5]. Each country reports to the WHO Intercountry Support Team (IST) for West Africa, the data is stored in a central database, and a surveillance bulletin is disseminated each week in the meningitis season (weeks 1-26) and monthly the rest of the year.

The phased introduction of a group A meningococcal conjugate vaccine, PsA-TT (MenAfriVac®) through mass vaccination campaigns targeting 1-29 year olds into the 26 countries of the African meningitis belt started in 2010, with the aim of completing the campaigns in 2017[6]. Countries are now planning for the introduction of MenAfriVac into the routine Expanded Programme on Immunization (EPI) schedule between the ages of 9 and 18 months[7]. This vaccine offers the hope of eliminating group A epidemics as a public health problem in Africa[8]. A report on meningitis incidence trends in the meningitis belt from 2004 until 2013 was recently published[5], but this analysis did not take account of the year of introduction of MenAfriVac® . We present a model of vaccine impact on the incidence of suspected and confirmed cases of meningitis in nine countries of the meningitis belt. This analysis takes account of the timing of vaccine introduction and extends the period of evaluation through 2015.

Methods

Definitions

Suspected meningitis case. Any person with sudden onset of fever (>38.5°C rectal or 38.0°C axillary) and one of the following signs: neck stiffness, flaccid neck (infants), bulging fontanelle (infants), convulsion or other meningeal signs[9].

Confirmed meningitis case. Any person with meningeal signs and isolation of a causal pathogen (*N. meningitidis* (Nm), *Streptococcus pneumoniae* (Spn), *Haemophilus influenzae* type b (Hib)) from the cerebrospinal fluid (CSF) by culture, polymerase chain reaction or rapid diagnostic test[9].

Data sources

An enhanced meningitis surveillance network was established across the meningitis belt in 2003[5]. Standard Operating Procedures, including standard case definitions (see above), intervention thresholds, laboratory standards and data collection tools were developed for surveillance officers, enabling them to use the same methods to detect and notify cases[10]. We included nine countries in the meningitis belt that introduced MenAfriVac® before 2014 and consistently submitted weekly district level surveillance reports of suspected meningitis cases to IST. We used data from Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Niger, and Togo from 2005 to 2015, data from Chad from 2006 onwards and data from Nigeria from 2007 onwards are also included. District level population estimates were submitted by each country in their surveillance reports. National level population was calculated as the sum of the district populations submitted to the WHO-IST.

In each year, the proportion of suspected cases that were confirmed was generally low. Given the paucity of confirmed cases at a weekly district level, we used data on confirmed cases at an annual country level, taken from the WHO bulletins at week 52 of each year for 2005 to 2015. The data on confirmed cases are not individually linked to the suspected case data..

For each country, details of the timing and targeted populations (if not a national campaign) for MenAfriVac® introduction were obtained from Meningitis Vaccine Project and WHO sources (summarised in Table S1). Vaccination on a district level was considered to be complete the week after the reported campaign ended. For laboratory confirmed cases, where data were only available annually at national level, the country-level vaccination status was categorised as unvaccinated (before the start of campaigns), partially vaccinated if campaigns were phased over more than one year or fully vaccinated the year following the completion of mass campaigns. We considered the time of vaccination relative to the meningitis season, e.g. Burkina Faso was considered unvaccinated in 2010 as the MenAfriVac® campaigns were conducted in December 2010 and nearly all of the data on meningitis were collected between January and June. Given that measures of vaccine uptake were universally high[11], and large indirect effects are expected[12,13], we did not adjust further for country level vaccination uptake (coverage) in the campaigns.

Prior to 2011, all but one country had introduced the Hib conjugate vaccine while no country had introduced pneumococcal conjugate vaccine (PCV)[14]. PCV was in use in the routine immunisation schedule by 2015 in Benin (year of introduction 2011), Burkina Faso (2013), Côte d'Ivoire (2014), Ghana (2012), Mali (2011), Niger (2014), and Togo (2014) (Table S1).

Data analysis

The primary outcome was the incidence rate ratio (IRR) of suspected meningitis cases in districts that had and had not been targeted for immunisation with MenAfriVac®. A negative binomial regression model was fitted to case counts at a weekly district level, with person years at risk based on the reported district population. The overall model adjusted for country *a priori*, and country-level IRR were also estimated. In a sensitivity analysis we just considered the cases occurring during the meningitis season, i.e. weeks 1-26, from 1st January of each year for all countries. We also used the data on suspected cases by district and week (for weeks 1-52) to measure the number of districts reaching the epidemic threshold of 10 per 100,000 during at least one week in a year for

both vaccinated and unvaccinated populations and calculated the relative risk. Incidence rate ratios for NmA disease and disease due to other meningococcal serogroups (nonA-Nm) were estimated for the laboratory confirmed cases, considering country-level vaccination status in three categories (unvaccinated, partially vaccinated and fully vaccinated as described above). As a check, we also examined IRR for pathogens other than *Neisseria meningitidis*, reported in the surveillance bulletins as Spn, Hib or 'Other'.

Role of the study sponsor

The sponsor of the study (WHO) supported the collection and curation of surveillance data and WHO employees named as authors contributed to study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Descriptive epidemiology

A total of 260,408 suspected meningitis cases were reported from the 9 countries between 2005 and 2015, with considerable variation by country and year (Table 1). The largest number of cases occurred in 2009 corresponding to a major epidemic in Nigeria and Niger, and the second largest peak in 2007 due to an epidemic in Burkina Faso. The proportion of confirmed cases rose to 19% (2778/14451) in 2015 from between 3-8% in the period 2005-2010 (Table 2).

The distribution of individual pathogens from confirmed cases of bacterial meningitis changed over the study period (Table 2). NmA was the main cause of meningitis until the roll-out of MenAfriVac® began in late 2010, with a peak of 1994 confirmed cases in 2009, when the majority (73%; 1456/1994) were from Niger. NmW was detected more frequently after 2010 than before, although a large epidemic of NmW in Burkina Faso occurred in 2002 before the study period [15]. An epidemic of NmX was recorded in Niger in 2006[3] and in 2010, NmX epidemics occurred in northern and central regions of Burkina Faso[16]. In 2015, there was a major epidemic of group C disease in Niger[17].

Epidemics of group C disease were also observed in some districts in Nigeria from 2013 onwards[2], but few cases were laboratory confirmed such that the Nigerian group C outbreaks are not well represented in Table 2. Spn remained an important cause of meningitis throughout the study period and there were relatively few cases of Hib or other pathogens, excepting 2015, when ~~nearly~~ 68~~70~~% (143~~of the~~ /210) of the 'other' pathogens were reported from Benin (which were incompletely characterised as gram stain positive bacteria).

Impact of MenAfriVac®

We estimate that the introduction of MenAfriVac® resulted in a 57% (95%CI 55-59%) decline in incidence of suspected meningitis cases overall (Table 3). There was a decline of 60% (95%CI 58-62%) considering just those cases occurring in the meningitis season. The impact of vaccine introduction varied by country. Reductions in the incidence of suspected cases were observed after vaccination in 7 out of 9 countries from the largest 91% reduction (95%CI 90- 92%) in Chad to 35% reduction (95%CI 29-42%) in Niger, where the overall effect of MenAfriVac® on suspected cases was moderated by the 2015 group C epidemic. There was an increase in the incidence rate ratio in Benin (IRR 4.04, 95%CI 3.56, 4.59) and Ghana (IRR 1.64, 95% CI 1.36, 1.98). Both countries experienced fewer than 1200 suspected cases per year, with a mean of 510 (Benin) and 544 (Ghana). The results are not driven by a particular district in either country. The more specific data on laboratory confirmed cases for these countries do not indicate an increase in any specific pathogen, with very few NmA cases after 2010. Excluding Benin and Ghana from the regression model leads to a greater impact estimate of 70% reduction in suspected meningitis cases after vaccine introduction (IRR 0.3, 95% CI 0.29, 0.31).

Examining the number of districts that reach the epidemic threshold of 10 per 100,000 per week in at least one week per year also demonstrates a significant impact of MenAfriVac®. In unvaccinated populations, the epidemic threshold was reached in 494/9345 districts compared to only 46/2170 districts in vaccinated populations, giving a relative risk of 0.41 (95% CI 0.31, 0.56), i.e. the risk of a

district reaching the epidemic threshold in at least one week of the year is approximately 60% lower in vaccinated compared to unvaccinated populations.

The number of confirmed NmA cases declined dramatically following the introduction of MenAfriVac® (Figure 1). Between 2011 and 2015 only 168 cases of NmA were confirmed overall, with only 9 reported in countries that had completed their MenAfriVac® campaigns. There was a dramatic decline in confirmed NmA overall, with an incidence rate ratio before and after vaccination for NmA of 0.06 (95% CI 0.01, 0.39) for partially vaccinated populations and 0.002 (95% CI 0.000, 0.009) for "fully vaccinated" populations; i.e. >99% decline in confirmed NmA in countries that have completed MenAfriVac® campaigns.

The number of cases due to *N. meningitidis* serogroups other than A increased after MenAfriVac® introduction (Figure 1). The incidence rate ratio for non-A Nm serogroups before and after vaccination was 2.48 (95% CI 0.68, 9.09) for partially vaccinated and 2.76 (95% CI 1.21, 6.30) for fully vaccinated populations. Outbreaks of NmW occurred in Burkina Faso after MenAfriVac® introduction in 2012 and there was a large NmC outbreak in Niger & Nigeria in 2015 (Table 2). However, outbreaks due to serogroups other than A were observed before MenAfriVac introduction (Figure 1, Table 2). If we remove the largest non-NmA outbreak (Niger, group C, 2015) then the IRR for "fully vaccinated" populations reduces to 2.39 (95% CI 0.98, 5.84), where the lower limit of the confidence interval is less than 1.

In terms of other meningitis pathogens, of which the majority are Spn, there was no significant change before and after MenAfriVac® introduction over the study period (IRR 0.91 95% CI 0.59, 1.43).

Discussion

The introduction of MenAfriVac® into the meningitis belt through mass immunisation campaigns of 1-29 year olds has had a dramatic impact on the incidence of suspected and confirmed meningitis cases. A consistent and substantial reduction was seen on confirmed NmA cases, with only 9 cases occurring in countries after the completion of mass campaigns. We estimated that the incidence of suspected meningitis cases fell by around 60% in vaccinated compared to unvaccinated populations. We found a similar decline in the number of districts reaching the epidemic threshold. There was an increase in the incidence rate ratio of meningococcal serogroups other than A.

This is the first multi-country study to estimate the impact of MenAfriVac®. It was not possible to include all countries in the meningitis belt because not all countries have consistently reported to IST over the study period and not all had introduced MenAfriVac® by 2014. In the nine included countries, substantial efforts have been made to improve data quality, as evidenced by the increasing proportions of suspected cases that are confirmed. Nevertheless, data quality remains a concern and poses challenges for the interpretation of the surveillance data. For example, in Benin and Ghana, the incidence rate ratio for suspected meningitis cases was higher post-MenAfriVac®. Since the number of suspected cases was relatively low and the confirmed case data show no group A disease after vaccine introduction and a mix of other pathogens, it is likely that this reflects improvements in the sensitivity of surveillance over time rather than a genuine increase in disease. Excluding these two countries increased the estimated impact on suspected cases to 70% reduction. As we were not able to quantify surveillance quality, this could not be formally included in the regression models; the relatively narrow confidence intervals around our incidence rate ratios may therefore be somewhat artificial. Initiatives to further improve surveillance, such as MenAfriNet, which supports meningitis case-based surveillance in Burkina Faso, Chad, Mali, Niger and Togo, are ongoing. Encouragement is being given to improve surveillance and reporting in the other 17 countries not included in these analyses but among the total of 26 countries targeted for

MenAfriVac immunisation. Our analyses accounted for the timing of vaccine introduction at a country and district level, but did not include measures of vaccine uptake. This information is often not confirmed at district level, and vaccine uptake was reported as exceptionally high[11].

We observed an increase over time in the incidence rate ratio of confirmed cases due to other (non-A) meningococcal serogroups in vaccinated compared to previously unvaccinated populations. The emergence of a novel serogroup C strain causing epidemics in Niger[18] and Nigeria[2] is a key event, and indeed the IRR decreases if the data from the epidemic in Niger in 2015 are removed. The extent to which the observed increases in non-A serogroups are an artefact of improved surveillance, a reflection of the dynamic nature of meningococcal infection or a phenomenon associated with selective vaccine introduction is not clear. Serotype replacement has been important for 7-and 13-valent pneumococcal conjugate vaccines[19], but replacement with non-vaccine types has not been observed for Hib or MenC conjugate vaccines[20]. Although MenAfriVac® reduces carriage of serogroup A[12,13] , carriage of serogroup A across the meningitis belt before vaccine introduction was infrequent[13,21], as observed with MenC in the UK. This means that any ecological niche in the pharynx left by serogroup A is small, which may offer minimal opportunity for replacement. Another possible mechanism for serogroup C to emerge as a direct result of MenAfriVac introduction and subsequent selection pressures would be capsule switching from group A to C. However, this does not seem to have occurred as the serogoup C clone in Niger and Nigeria is completely novel, it was first isolated in non-vaccinated districts, and there are no known group A strains with the same unusual porA (P1.21-15,16) and sequence type (ST-10217) either in disease or carriage isolates. Furthermore, Nm assigned to ST-5 clonal complex, especially ST-7 and ST-2859, have not been found with a capsule other than A. Given the temporal variability in both incidence and the predominant outbreak strains before MenAfriVac® introduction, and further evidence on the dynamic nature of meningococcal carriage in Africa[21] it seems that the most likely explanation is that these increases are due to natural ecological changes. Improvements in reporting and confirmation of cases over time may also have contributed to this finding, but we did not have any metrics on surveillance

quality to include in our statistical model. Interestingly there was no increase in reporting of meningitis due to other pathogens before and after MenAfriVac® introduction (IRR 0.91 95% CI 0.59, 1.43), as this in some way serves as a negative control for our studies of primarily meningococcal meningitis. (Note that in all countries except Chad, PCV was introduced into the routine infant immunisation programme between 2011 and 2015. As the vaccine is given only to infants, and the vaccinated cohorts currently make up a small proportion of the population, this is unlikely to have had substantial population level effects on pneumococcal meningitis incidence.) Given the long term irregular fluctuations in meningitis incidence across the meningitis belt, analysis of trends would ideally have included longer periods of analysis before and after vaccine introduction. Ongoing, good quality surveillance is essential to fully understand vaccine impact, including replacement.

The success of MenAfriVac® as a model of public-private vaccine development to meet a pressing public health need is already assured[8]. These findings illustrate the health impact of this vaccine. This is seen in both the reduction in disease burden as measured in numbers of cases, but also through the reduced risk of epidemics on a district level, which are hugely disruptive to general health services as well as to communities. It is crucial to build on this success by completing the roll-out of mass campaigns and rapidly incorporating MenAfriVac® into routine EPI[22]. Improving the capacity to thoroughly investigate and document any cases of NmA in vaccinated areas is important for ongoing monitoring which will enable the post-MenAfriVac® reality to be fully appreciated. This will also allow the effects of other vaccines (such as Hib or pneumococcal) on meningitis trends to be further documented. There are however, some signs for caution, particularly in the observation of epidemics due to other meningococcal serogroups. This further highlights the need for continued vigilance and high quality surveillance. The WHO guidelines on epidemic meningitis, which were revised in the light of the declining burden of NmA, have implemented a lower alert threshold of 3 per 100,000 per week (from 5 per 100,000 per week) to improve preparedness and decrease response time in the event of an epidemic. Improvements in clinical care could also reduce the

mortality from meningitis[23]. In the longer term, there are prospects for multi-valent meningococcal conjugate vaccines, which are likely to be a valuable tool for the prevention of meningitis in countries at highest risk.

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Author contributions

JMS, OR, KF and MPP conceived the study idea. CL collated the surveillance data. AB, CTB, MPP and CLT collated the vaccination data. CLT and LVC performed the statistical analyses. CLT and JMS wrote the first draft. All authors interpreted the findings, critically reviewed the draft manuscripts and approved the final version.

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Declaration of interests

CLT reports personal fees from GSK and Sanofi Pasteur, outside the submitted work; all other authors declare no conflicts of interest.

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Research in context

Evidence before this study

We searched PubMed in October 2016 for papers on MenAfriVac® impact using the search terms ("MenAfriVac" OR "PsA-TT") AND ("disease" OR "carriage") AND ("Africa" OR "meningitis belt") and reports submitted to MVP. Publication dates and languages were not limited. Prior to this study, evidence that MenAfriVac® was effective against both meningitis and group A carriage had been reported from Chad and Burkina Faso. A previous report on surveillance data in 10 countries reporting to WHO's Inter-country support team in Burkina Faso showed a dramatic fall in NmA disease after the introduction of MenAfriVac® to 2013 but did not include a robust statistical analysis.

Added value of this study

This is the first multi-country description and robust statistical analysis of the impact of MenAfriVac®. The study provides evidence that the overall burden of suspected meningitis is reduced by around 60%, that NmA is confirmed very rarely in vaccinated populations and that meningitis caused by other meningococcal serogroups and other pathogens remains a concern.

Implications of all the available evidence

Given the observed impact on meningitis, this study supports the continued roll-out of MenAfriVac® and incorporation into the routine immunisation schedule of affected countries. Continued efforts to strengthen meningitis surveillance and outbreak response in the meningitis belt are required. There is a need for multi-valent meningococcal conjugate vaccines to further reduce the burden of epidemic meningitis.

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Legends for figures and tables

Figure 1: Total annual suspected and confirmed cases of bacterial meningitis across all 7 countries in relation to MenAfriVac introduction (dotted line).

Table 1: Suspected meningitis cases by year in nine countries of the African meningitis belt, 2005-2015.

Table 2: Confirmed Meningitis Cases and Organisms isolated from CSF in nine countries of the African Meningitis Belt, 2005–2015

Table 3: Impact of MenAfriVac® on suspected cases of meningitis reported by district and week. Incidence rate ratios (IRR) comparing vaccinated to unvaccinated time periods.

Figure S1: Annual incidence of suspected and confirmed cases of bacterial meningitis per 100,000 by country. Year of MenAfriVac introduction indicated by dotted line.

Figure S2: Annual incidence of confirmed cases of group A meningococcal, non-A meningococcal, and other bacterial meningitis per 100,000 by country. Year of MenAfriVac introduction indicated by dotted line.

Table S1: Timing of vaccine introduction for MenAfriVac® (campaigns of 1-29 year olds), routine infant pneumococcal conjugate vaccine (PCV), and routine infant Hib conjugate vaccine by country.